

RESEARCH

Open Access



Association between serum uric acid levels and bone mineral density in patients with osteoporosis: a cross-sectional study

Min-zhe Xu^{1†}, Ke Lu^{1†}, Xu-feng Yang¹, Yao-wei Ye², Si-ming Xu², Qin Shi³, Ya-qin Gong⁴ and Chong Li^{1*}

Abstract

Background The results of studies exploring the association between serum uric acid (SUA) and bone mineral density (BMD) have been controversial and inconsistent. We thus sought to explore whether SUA levels were independently associated with BMD in patients with osteoporosis (OP).

Methods This cross-sectional analysis was conducted using prospectively obtained data from the Affiliated Kunshan Hospital of Jiangsu University database pertaining to 1,249 OP patients that were hospitalized from January 2015 – March 2022. BMD was the outcome variable for this study, while baseline SUA levels were the exposure variable. Analyses were adjusted for a range of covariates including age, gender, body mass index (BMI) and a range of other baseline laboratory and clinical findings.

Results SUA levels and BMD were independently positively associated with one another in OP patients. Following adjustment for age, gender, BMI, blood urae nitrogen (BUN), and 25(OH)D levels, a 0.0286 g/cm² (β , 0.0286; 95% confidence interval [CI], 0.0193—0.0378, $P < 0.000001$) increase in BMD was observed per 100 μ mol/L rise in SUA levels. A non-linear association between SUA and BMD was also observed for patients with a BMI < 24 kg/m², with a SUA level inflection point at 296 μ mol/L in the adjusted smoothed curve.

Conclusions These analyses revealed SUA levels to be independently positively associated with BMD in OP patients, with an additional non-linear relationship between these two variables being evident for individuals of normal or low body weight. This suggests that SUA levels may exert a protective effect on BMD at concentrations below 296 μ mol/L in normal- and low-weight OP patients, whereas SUA levels above this concentration were unrelated to BMD.

Keywords Osteoporosis, Uric acid, Bone mineral density, Threshold effect

[†]Min-zhe Xu and Ke Lu contributed equally to this work and should be considered co-first authors.

*Correspondence:

Chong Li

lichong1705@163.com

Full list of author information is available at the end of the article



Background

Osteoporosis (OP) is a form of chronic progressive metabolic disease that results in the aberrant loss of bone mass and concomitant microstructural deterioration within the bone tissue, ultimately increasing the fragility of these bones and increasing the risk of fracture [1]. Low bone mineral density (BMD) was associated with an estimated 438,000 deaths and 16.6 million disability-adjusted life years in 2019, corresponding to respective 111.1% and 93.8% increases relative to 1990. Rising rates of disability and death associated with low BMD have been observed in China, Australia, Canada, and the USA, among other countries [2], and these rising rates of OP have imposed a growing social and economic burden on affected populations [3]. Efforts to define factors that can reduce the risk of OP and improve overall bone health are thus critical to global public health.

Humans exhibit high levels of several different natural antioxidants including albumin, bilirubin, and uric acid. Of these, uric acid is the most abundant, with heterocyclic serum uric acid (SUA) composed of carbon, hydrogen, oxygen, and nitrogen being produced as the final byproduct of human purine metabolism. SUA has been suggested in some reports to have a beneficial impact on BMD [4–8], with its putative benefits being attributed to its robust antioxidant activity in vivo and in vitro [9, 10]. Specifically, the antioxidant activity of SUA enables it to suppress osteoclast-mediated bone resorption and to promote osteoblastogenesis, thus enhancing BMD [11]. Reactive oxygen species (ROS) including hydroxyl radicals and singlet oxygen can contribute to reductions in BMD, and the ability of SUA to mitigate such stress may enable it to play a protective role in OP.

Recent work has sought to explore the association between SUA and BMD, but the results of these studies have been controversial and inconsistent. While some work suggests that high SUA levels can exert a protective impact on BMD [12], other work has revealed no relationship between SUA and BMD in the lumbar spine [13]. Given current uncertainty regarding the relationship between these clinical variables, this study was designed to explore relationships between SUA and BMD in a representative population of hospitalized OP patients.

Materials and methods

Study design and subjects

OP is diagnosed based on the observation of fragility-associated fractures when no other metabolic bone disorders are evident, even when BMD (T-score) is normal, or by a T score ≤ -2.5 for the lumbar spine, femoral neck, total hip, or 1/3 radius (33% radius) even when fractures are not evident. Osteoporotic fractures (OPFs), also

referred to as fragility fractures, are caused by low-energy mechanisms, such as falls from standing height or below. The most severe OPFs are hip fractures. Additional low-trauma fractures that are regarded as OPFs include certain distal forearm fractures, proximal humerus fractures, vertebral fractures, and pelvic fractures [14]. OP cases are separated into primary and secondary OP [15]. Postmenopausal, age-related, and idiopathic OP are the three subtypes of primary OP [16]. The term "secondary osteoporosis" refers to bone loss brought on by specific, well-defined clinical diseases [17]. The present study enrolled consecutive hospitalized primary OP patients with definitive diagnoses. In total, 2,157 consecutive hospitalized primary OP patients were evaluated for study inclusion (Fig. 1). Patients were excluded if they were under 18 years old, if their SUA or BMD data were missing, if they exhibited extreme BMD or SUA values, or if they were taking drugs with the potential to impact SUA levels. In total, 1,249 patients were ultimately included in the present analysis based on these criteria. Since Zoledronic acid (ZOL) was being administered to all of these individuals for the first time, the impact of bisphosphonates on BMD may be disregarded. These patients exhibited a mean (\pm SD) level of 288.61 ± 83.79 $\mu\text{mol/L}$, and were stratified into four SUA quartiles: Q1, < 231 $\mu\text{mol/L}$; Q2, 231 – 278 $\mu\text{mol/L}$; Q3, 278 – 341 $\mu\text{mol/L}$, and Q4, > 341 $\mu\text{mol/L}$. The Affiliated Kunshan Hospital of Jiangsu University approved this study (approval No. 2020–03-046-K01), which was consistent with the Declaration of Helsinki. Patient data were initially recorded for the improvement of hospital quality, with all analyses being conducted by individuals blinded to patient identity. As this was an observational study and data were gathered anonymously, written informed consent was not required for these analyses. The informed consent was waived by the Ethics Committee of the Affiliated Kunshan Hospital of Jiangsu University.

Exposure and outcome variables

SUA levels, as measured via an enzymatic colorimetric method before ZOL injection between January 2015 and March 2022, were the exposure variable in this study. Lumbar spine BMD, as measured via dual-energy X-ray absorptiometry (DXA) with a Hologic dual-energy X-ray bone density instrument (Discovery Wi, Hologic Inc, USA), was the outcome variable for this study. The same instrument and the same experienced operator were used to collect all measurements through the use of standardized procedures. Each day prior to participant examination, the machine was subject to standard quality control procedures. Lumbar spine BMD values (g/cm^2) were based on data from the first, second, third, and fourth lumbar vertebra.

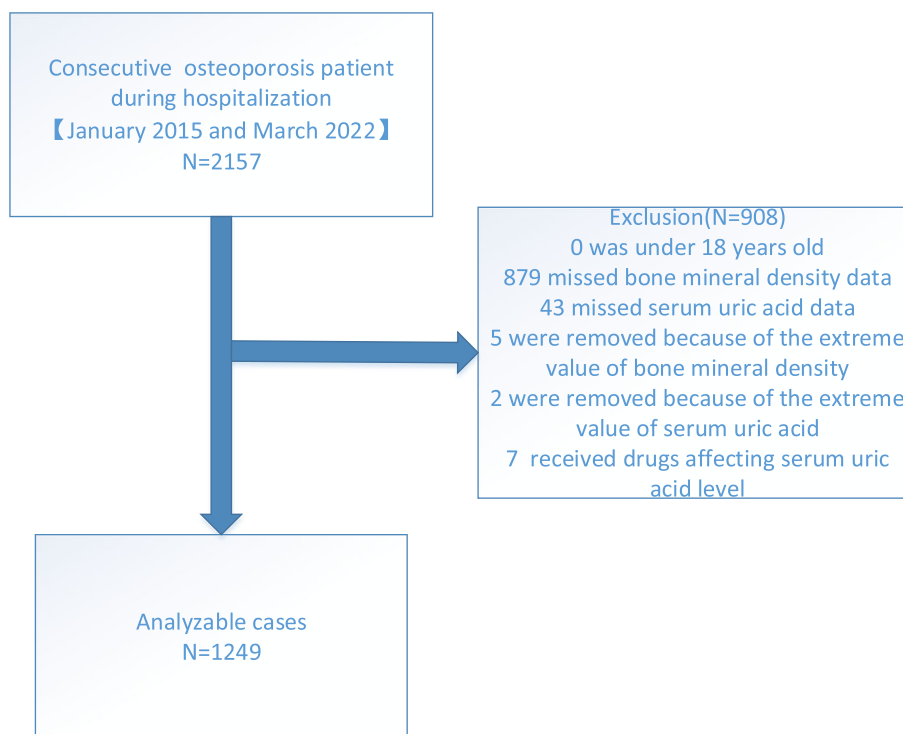


Fig. 1 Study flow chart

Covariate analyses

Many different potential covariates were analyzed in the present study, including age, gender, BMI (weight/height²; overweight: 24–27.9 kg/m², obese: ≥ 28 kg/m² based on a meta-analysis organized by the Working Group on Obesity in China [18]), Charlson comorbidity index (CCI, [19]) score, primary diagnosis (OP without fractures/OPF), calcitonin use, surgery (yes/no), hemoglobin, monocyte count, lymphocyte count, platelet count, neutrophil count, triglycerides, total cholesterol, albumin, calcium, AST (aspartate aminotransferase), ALT (alanine aminotransferase), creatinine (Cr), blood urea nitrogen (BUN), low-density lipoprotein, high-density lipoprotein, apolipoprotein A, apolipoprotein B, homocysteine, glucose, and 25(OH)D (25-hydroxy vitamin D) levels. All blood samples were collected from fasting patients. Calcitonin use was defined by the intramuscular or subcutaneous administration of 50 IU calcitonin per day. Surgery was defined by hospitalization due to fragility fractures.

Statistical analyses

Continuous demographic, laboratory, and clinical data are presented as means with standard deviations (SD) or medians (25th, 75th), while categorical data are presented in the form of frequencies (percentages). Pearson’s chi-square tests or Fisher’s exact tests were used for

univariate analyses of categorical data, while continuous data were compared using independent sample t-tests and Mann–Whitney U tests when normally and non-normally distributed, respectively. Associations between OP patient characteristics and BMD were also examined through univariate analyses.

Independent relationships between SUA levels and BMD in patients with OP were explored using generalized estimating equations (GEE) with appropriate adjustment for covariates. Developed models included unadjusted and minimally adjusted models (Model 1 and Model 2, respectively) as well as fully-adjusted models (Model 3/4). Initially, variance inflation factor (VIF) analyses were used to detect the collinearity of covariance, after which the decision to adjust for these covariates was made based on the following criteria: (1) a change in the matched odds ratio (OR) of ≥ 10% was observed when the covariate was added to the basic model or removed from the full model; (2) covariates meeting criterion 1 or covariates exhibiting a *P* < 0.1 in univariate models [20]. Model 3 and Model 4 were respectively developed using Criterion 1 and Criterion 2 for covariate adjustment. Finally, four models were established, as follows: Model 1 was unadjusted; Model 2 (minimally adjusted model) was adjusted for age, gender, BMI, and 25(OH)D levels; Model 3 was adjusted for age, gender, BMI, 25(OH)D levels, and BUN; Model

4 was adjusted for age, gender, BMI, 25(OH)D levels, primary diagnosis, BUN, ALT, AST, and Cr.

A generalized additive model (GAM) was used to detect potential non-linear correlative relationships. When such relationships were evident, a two-piecewise linear regression model was used to identify threshold effects for the resultant smoothing curves. A recursive method was used to automatically calculate the inflection point using a maximum likelihood model when these curves exhibited a clear ratio [21]. The robustness of these analyses and their variations among patient subgroups were performed by repeating subgroup analyses when patients were stratified based on particular covariates, with the likelihood ratio test (LRT) being used to analyze subgroup interactions and modifications.

R packages (<http://www.R-project.org>, The R Foundation) and EmpowerStats (<http://www.empowerstats.com>, X&Y Solutions, Inc, MA, USA) were used for all analyses, with a two-sided $P < 0.05$ as the significance threshold.

Results

Patient characteristics

Baseline characteristics for patients with OP hospitalized from January 2015 – March 2022 ($n = 1,249$) in the established SUA quartiles are summarized in Table 1. These patients (18.65% male, 81.35% female) exhibited an average age of 67.94 ± 9.61 years. The mean BMD for these patients was 0.76 ± 0.14 g/cm², while the mean SUA was 288.61 ± 83.79 μ mol/L in the overall patient population. Patients were stratified into SUA quartiles (< 231 μ mol/L, 231–278 μ mol/L, 278–341 μ mol/L, and > 341 μ mol/L), and differences in BMD, platelet count, lymphocyte count, albumin, calcium, ALT, AST, Cr, BUN, glucose, triglyceride, high-density lipoprotein, low-density lipoprotein, apolipoprotein A, homocysteine, 25(OH)D levels, gender, BMI, calcitonin use, surgery, and primary diagnosis were evident among these quartiles. Specifically, patients in higher SUA quartiles were more likely to exhibit higher BMD (Q1: 0.71 ± 0.12 g/cm²; Q2: 0.75 ± 0.13 g/cm²; Q3: 0.78 ± 0.14 g/cm²; Q4: 0.80 ± 0.15 g/cm², $P < 0.001$).

Univariate analyses of factors associated with BMD

In univariate analyses, a clear relationship was observed between BMD and variables including gender, age, BMI, neutrophil count, lymphocyte count, monocyte count, albumin, hemoglobin, ALT, AST, Cr, triglyceride, 25(OH)D levels, calcitonin use, primary diagnosis, and SUA levels (Table 2). No other analyzed variables were related to BMD in these OP patients.

Exploration of the association between SUA levels and BMD

Four models were next used to examine the relationship between SUA and BMD in OP patients (Table 3). A clear relationship between these variables was evident in the unadjusted Model 1 ($\beta = 0.0440$, 95% CI: 0.0350 to 0.0530, $P < 0.000001$). Model 2, which was adjusted for age, gender, BMI, and 25(OH)D levels, exhibited a similar association ($\beta = 0.0288$, 95% CI: 0.0199 to 0.0377, $P < 0.000001$). A positive relationship was also evident for Model 3 ($\beta = 0.0286$, 95% CI: 0.0193 to 0.0378, $P < 0.000001$) following adjustment for age, gender, BMI, 25(OH)D levels, and BUN. Model 4, which was adjusted for age, gender, BMI, 25(OH)D levels, primary diagnosis, BUN, ALT, AST, and Cr, also yielded a similar relationship between these variables ($\beta = 0.0235$, 95% CI: 0.0139 to 0.0330, $P = 0.000002$).

SUA levels were used to group patients into quartiles, revealing average BMD values that were 0.0163 g/cm², 0.0445 g/cm², and 0.0547 g/cm² units higher in Q2, Q3, and Q4 relative to Q1 in Model 3. Marked increases in BMD were evident for OP patients in SUA quartiles 3 and 4 under all four models, and in Model 1, BMD levels were higher in Q2 relative to Q1.

To confirm the robustness of Model 3, subgroup analyses were further conducted in which OP patients were stratified according to age, gender, BMI, 25(OH)D levels, and BUN, with analyses being adjusted for the remaining covariates not used for stratification. A highly consistent pattern was observed across these results without any apparent stratification-related interactions (all $P > 0.05$, Table S1). As shown in Fig. S1, relationships between SUA and BMD were consistent in both males and females when adjusting for age, BMI, 25(OH)D levels, and BUN.

Spline smoothing plot and threshold analyses

A graphical approach was next used to represent estimated exposure–response plots for OP patients stratified according to BMI status in an effort to gauge whether the relationship between SUA levels and BMD was linear or non-linear (Fig. 2). GAM estimation suggested the existence of a non-linear relationship between SUA and BMD for patients with a BMI < 24 kg/m² (P -value for LRT = 0.034) following adjustment for age, gender, 25(OH)D levels, and BUN (Table 4). In these normal- and low-weight patients with OP, a threshold non-linear association was detected between SUA levels and BMD, with an inflection point ($K = 2.96$) being established with a piecewise linear regression model. To the left of this inflection point, the respective effect size, 95% CI, and P -values were 0.0438, 0.0217–0.0658, and 0.0001. To the right of this inflection point, SUA levels were unrelated to

Table 1 Patient characteristics based on SUA quartiles

Characteristics	Total	Mean ± SD / N (%)				P-value	P-value*
		Q1(< 231 μmol/L)	Q2(231–278 μmol/L)	Q3(278–341 μmol/L)	Q4(> 341 μmol/L)		
N	1249	311	311	313	314		
BMD, g/cm ²	0.76 ± 0.14	0.71 ± 0.12	0.75 ± 0.13	0.78 ± 0.14	0.80 ± 0.15	< 0.001	< 0.001
Age, y	67.94 ± 9.61	68.28 ± 8.69	66.90 ± 9.61	67.74 ± 9.31	68.83 ± 10.66	0.076	0.053
Platelet count, × 10 ⁹ /L	185.12 ± 61.04	185.08 ± 64.99	191.84 ± 58.52	181.59 ± 53.16	181.98 ± 66.29	0.133	0.045
Neutrophil count, × 10 ⁹ /L	4.47 ± 2.35	4.38 ± 2.12	4.51 ± 2.42	4.35 ± 2.39	4.66 ± 2.44	0.355	0.206
Lymphocyte count, × 10 ⁹ /L	1.41 ± 0.56	1.27 ± 0.50	1.40 ± 0.54	1.48 ± 0.59	1.47 ± 0.58	< 0.001	< 0.001
Monocyte count, × 10 ⁹ /L	0.41 ± 0.19	0.40 ± 0.17	0.41 ± 0.18	0.40 ± 0.20	0.43 ± 0.20	0.168	0.257
Albumin, g/L	40.26 ± 4.75	39.76 ± 4.37	40.61 ± 4.65	40.58 ± 4.69	40.07 ± 5.21	0.070	0.013
Hemoglobin, g/L	124.20 ± 16.72	121.98 ± 18.46	125.07 ± 14.24	125.26 ± 14.39	124.47 ± 19.04	0.055	0.065
Calcium, mmol/L	2.27 ± 0.18	2.24 ± 0.22	2.27 ± 0.15	2.28 ± 0.13	2.28 ± 0.20	0.012	< 0.001
ALT, U/L	21.14 ± 13.59	18.85 ± 10.84	20.56 ± 13.62	21.04 ± 11.96	24.09 ± 16.72	< 0.001	< 0.001
AST, U/L	23.82 ± 10.68	21.99 ± 8.27	23.37 ± 9.82	23.93 ± 9.93	25.96 ± 13.61	< 0.001	0.002
Cr, μmol/L	61.39 ± 24.98	54.87 ± 19.63	55.32 ± 12.87	60.61 ± 18.73	74.66 ± 36.56	< 0.001	< 0.001
CRP, mg/L	1.66 ± 4.60	1.35 ± 3.10	1.75 ± 3.56	1.51 ± 3.49	2.05 ± 7.10	0.760	0.762
BUN, mmol/L	6.24 ± 1.82	5.76 ± 1.45	5.83 ± 1.45	6.33 ± 1.60	7.03 ± 2.33	< 0.001	< 0.001
Glucose, mmol/L	6.06 ± 1.95	6.32 ± 2.14	6.12 ± 2.01	5.88 ± 1.62	5.92 ± 1.96	0.019	0.041
Total cholesterol, mmol/L	4.58 ± 1.01	4.52 ± 1.04	4.71 ± 1.05	4.54 ± 0.95	4.56 ± 0.99	0.166	0.110
Triglyceride, mmol/L	1.38 ± 0.93	1.22 ± 1.12	1.30 ± 0.72	1.37 ± 0.82	1.60 ± 0.98	< 0.001	< 0.001
High-density lipoprotein, mmol/L	1.46 ± 0.33	1.50 ± 0.33	1.52 ± 0.33	1.45 ± 0.35	1.40 ± 0.30	< 0.001	< 0.001
Low-density lipoprotein, mmol/L	2.74 ± 0.81	2.63 ± 0.85	2.80 ± 0.79	2.71 ± 0.78	2.82 ± 0.80	0.056	0.040
Apolipoprotein A, g/L	1.38 ± 0.27	1.38 ± 0.27	1.42 ± 0.29	1.36 ± 0.27	1.35 ± 0.26	0.038	0.030
Apolipoprotein B, g/L	0.90 ± 0.24	0.87 ± 0.25	0.92 ± 0.24	0.89 ± 0.23	0.91 ± 0.23	0.085	0.076
Homocysteine, μmol/L	13.12 ± 6.80	11.34 ± 4.91	12.50 ± 7.03	12.88 ± 5.46	15.44 ± 8.39	< 0.001	< 0.001
25(OH)D levels, ng/mL	20.81 ± 8.19	18.52 ± 7.41	21.25 ± 8.20	20.89 ± 7.81	22.59 ± 8.79	< 0.001	< 0.001
Gender, N (%)						< 0.001	-
Male	233 (18.65%)	25 (8.04%)	46 (14.79%)	64 (20.45%)	98 (31.21%)		
Female	1016 (81.35%)	286 (91.96%)	265 (85.21%)	249 (79.55%)	216 (68.79%)		
BMI categorical, N (%)						< 0.001	-
< 24 kg/m ²	778 (62.29%)	223 (71.70%)	206 (66.24%)	186 (59.42%)	163 (51.91%)		
24–28 kg/m ²	358 (28.66%)	75 (24.12%)	85 (27.33%)	100 (31.95%)	98 (31.21%)		
≥ 28 kg/m ²	113 (9.05%)	13 (4.18%)	20 (6.43%)	27 (8.63%)	53 (16.88%)		
CCI score categorical, N (%)						0.197	-
0	879 (70.38%)	234 (75.24%)	224 (72.03%)	209 (66.77%)	212 (67.52%)		
1–2	194 (15.53%)	47 (15.11%)	39 (12.54%)	53 (16.93%)	55 (17.52%)		
3–4	107 (8.57%)	17 (5.47%)	28 (9.00%)	34 (10.86%)	28 (8.92%)		
≥ 5	69 (5.52%)	13 (4.18%)	20 (6.43%)	17 (5.43%)	19 (6.05%)		
Calcitonin usage, N (%)						0.017	-
No	973 (77.90%)	223 (71.70%)	243 (78.14%)	254 (81.15%)	253 (80.57%)		
Yes	276 (22.10%)	88 (28.30%)	68 (21.86%)	59 (18.85%)	61 (19.43%)		
Surgery, N (%)						< 0.001	-
No	636 (50.92%)	119 (38.26%)	162 (52.09%)	179 (57.19%)	176 (56.05%)		
Yes	613 (49.08%)	192 (61.74%)	149 (47.91%)	134 (42.81%)	138 (43.95%)		
Primary diagnosis, N (%)						< 0.001	-
OP without fractures	771 (61.73%)	151 (48.55%)	193 (62.06%)	213 (68.05%)	214 (68.15%)		
OPF	478 (38.27%)	160 (51.45%)	118 (37.94%)	100 (31.95%)	100 (31.85%)		

Abbreviations: SUA serum uric acid, SD standard deviation, Q1 first quartile, Q2 second quartile, Q3 third quartile, Q4 fourth quartile, BMD bone mineral density, ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine, CRP C-reactive protein, BUN blood urea nitrogen, 25(OH)D 25-hydroxy vitamin D, BMI body mass index, CCI Charlson comorbidity index, OP osteoporosis, OPF osteoporotic fracture
P-value*: Kruskal Wallis Rank Test for continuous variables, Fisher Exact for categorical variables with Expects < 10

Table 2 Univariate analyses of factors associated with BMD

Characteristics	Statistics	β ^a (95% CI) P-value
Gender, N (%)		
Male	233 (18.6549%)	Reference
Female	1016 (81.3451%)	-0.1082 (-0.1274, -0.0891) < 0.000001
Age, y	67.9416 ± 9.6115	-0.0027 (-0.0035, -0.0019) < 0.000001
BMI categorical, N (%)		
< 24 kg/m ²	778 (62.2898%)	Reference
24–28 kg/m ²	358 (28.6629%)	0.0495 (0.0322, 0.0669) < 0.000001
≥ 28 kg/m ²	113 (9.0472%)	0.0650 (0.0376, 0.0923) 0.000004
Platelet count, × 10 ⁹ /L	185.1208 ± 61.0412	-0.0000 (-0.0002, 0.0001) 0.599814
Neutrophil count, × 10 ⁹ /L	4.4744 ± 2.3500	0.0043 (0.0009, 0.0076) 0.012360
Lymphocyte count, × 10 ⁹ /L	1.4060 ± 0.5580	0.0199 (0.0058, 0.0340) 0.005661
Monocyte count, × 10 ⁹ /L	0.4122 ± 0.1880	0.0467 (0.0049, 0.0885) 0.028736
Albumin, g/L	40.2558 ± 4.7470	0.0022 (0.0005, 0.0038) 0.009684
Hemoglobin, g/L	124.2002 ± 16.7161	0.0010 (0.0005, 0.0014) 0.000059
Calcium, mmol/L	2.2704 ± 0.1783	-0.0074 (-0.0514, 0.0365) 0.739645
ALT, U/L	21.1433 ± 13.5909	0.0015 (0.0009, 0.0020) < 0.000001
AST, U/L	23.8199 ± 10.6814	0.0011 (0.0004, 0.0018) 0.003639
Cr, μmol/L	61.3947 ± 24.9772	0.0008 (0.0005, 0.0012) < 0.000001
CRP, mg/L	1.6649 ± 4.6003	0.0029 (-0.0002, 0.0061) 0.068442
BUN, mmol/L	6.2376 ± 1.8168	0.0032 (-0.0011, 0.0075) 0.145362
Glucose, mmol/L	6.0574 ± 1.9495	-0.0004 (-0.0044, 0.0036) 0.854772
Total cholesterol, mmol/L	4.5818 ± 1.0068	0.0020 (-0.0069, 0.0109) 0.660990
Triglyceride, mmol/L	1.3796 ± 0.9285	0.0099 (0.0002, 0.0196) 0.044713
High-density lipoprotein, mmol/L	1.4647 ± 0.3296	-0.0236 (-0.0508, 0.0037) 0.090335
Low-density lipoprotein, mmol/L	2.7438 ± 0.8069	0.0089 (-0.0023, 0.0200) 0.118669
Apolipoprotein A, g/L	1.3769 ± 0.2728	-0.0105 (-0.0435, 0.0224) 0.530965
Apolipoprotein B, g/L	0.8986 ± 0.2364	0.0122 (-0.0258, 0.0502) 0.529786
Homocysteine, μmol/L	13.1186 ± 6.8044	0.0010 (-0.0003, 0.0023) 0.126096
25(OH)D levels, ng/mL	20.8138 ± 8.1942	0.0026 (0.0017, 0.0036) < 0.000001
CCI score categorical, N (%)		
0	879 (70.3763%)	Reference
1–2	194 (15.5324%)	-0.0172 (-0.0391, 0.0047) 0.124098
3–4	107 (8.5669%)	-0.0048 (-0.0331, 0.0235) 0.740577
≥ 5	69 (5.5244%)	-0.0124 (-0.0469, 0.0221) 0.481759
Calcitonin usage, N (%)		
No	973 (77.9023%)	Reference
Yes	276 (22.0977%)	-0.0259 (-0.0447, -0.0071) 0.007011
Surgery, N (%)		
No	636 (50.9207%)	Reference
Yes	613 (49.0793%)	0.0008 (-0.0149, 0.0164) 0.921790
Primary diagnosis, N (%)		
OP without fractures	771 (61.7294%)	Reference
OPF	478 (38.2706%)	-0.0334 (-0.0494, -0.0175) 0.000044
Serum uric acid, per 100 μmol/L increase	2.8861 ± 0.8379	0.0440 (0.0350, 0.0530) < 0.000001
Serum uric acid quartile, N (%)		
Q1 (< 232 μmol/L)	311 (24.8999%)	Reference
Q2 (232–280 μmol/L)	311 (24.8999%)	0.0327 (0.0113, 0.0542) 0.002863
Q3 (280–336 μmol/L)	313 (25.0600%)	0.0677 (0.0462, 0.0891) < 0.000001
Q4 (> 336 μmol/L)	314 (25.1401%)	0.0924 (0.0710, 0.1139) < 0.000001

Abbreviations: BMD bone mineral density, CI confidence interval, BMI body mass index, ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine, CRP C-reactin protein, BUN blood urea nitrogen, CCI Charlson comorbidity index, 25(OH)D 25-hydroxy vitamin D, OP osteoporosis, OPF osteoporotic fracture

^a Dependent variable BMD, as a result of univariate analyses for BMD

Table 3 Association between SUA levels and BMD in different models

	Model 1 ^a N = 1249 β (95%CI) P-value	Model 2 ^b N = 1249 β (95%CI) P-value	Model 3 ^c N = 1249 β (95%CI) P-value	Model 4 ^d N = 1249 β (95%CI) P-value
Serum uric acid per 100 μmol/L increase	0.0440 (0.0350, 0.0530) <0.000001	0.0288 (0.0199, 0.0377) <0.000001	0.0286 (0.0193, 0.0378) <0.000001	0.0235(0.0139, 0.0330) 0.000002
Serum uric acid quartile				
Q1(< 231 μmol/L)	Reference	Reference	Reference	Reference
Q2(231–278 μmol/L)	0.0327 (0.0113, 0.0542) 0.002863	0.0163 (-0.0038, 0.0365) 0.112425	0.0163 (-0.0039, 0.0364) 0.114381	0.0135 (-0.0066, 0.0337) 0.187813
Q3(278–341 μmol/L)	0.0677 (0.0462, 0.0891) <0.000001	0.0451 (0.0248, 0.0653) 0.000014	0.0445 (0.0241, 0.0649) 0.000020	0.0391 (0.0185, 0.0596) 0.000199
Q4(> 341 μmol/L)	0.0924 (0.0710, 0.1139) <0.000001	0.0558 (0.0348, 0.0769) <0.000001	0.0547 (0.0331, 0.0763) <0.000001	0.0428 (0.0207, 0.0650) 0.000153
P-value for trend	<0.000001	<0.000001	<0.000001	0.000034

Abbreviations: SUA serum uric acid, BMD bone mineral density, CI confidence interval, Q1 first quartile, Q2 second quartile, Q3 third quartile, Q4 fourth quartile, BMI body mass index, 25(OH)D 25-hydroxy vitamin D, BUN blood urea nitrogen, ALT alanine aminotransferase, AST aspartate aminotransferase, Cr creatinine

^a No adjustment

^b Adjusted for age, gender, BMI, 25(OH)D levels

^c Adjusted for age, gender, BMI, 25(OH)D levels, BUN

^d Adjusted for age, gender, BMI, 25(OH)D levels, primary diagnosis, BUN, ALT, AST, Cr

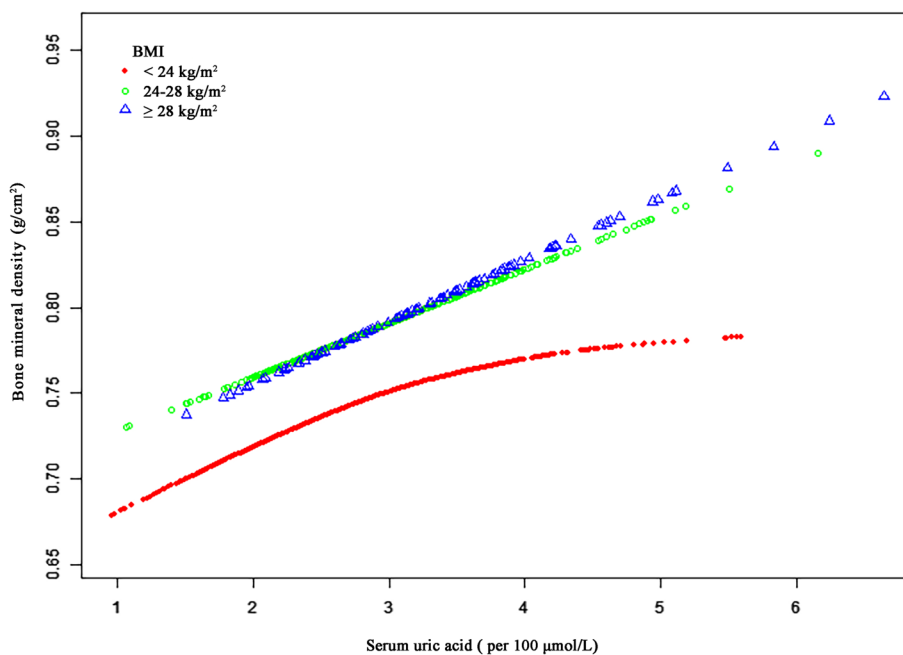


Fig. 2 The relationship between SUA and BMD. Adjusted smoothed curves corresponding to the relationship between SUA levels and BMD. A generalized additive model revealed a thresholded non-linear relationship between SUA and BMD in OP patients with a BMI < 24 kg/m². Red, green, and blue curves respectively correspond to estimated values for OP patients with a BMI < 24 kg/m², 24–28 kg/m², and > 28 kg/m². Models were adjusted for age, gender, 25(OH)D levels, and BUN. The red curve in Model 3 exhibited an inflection point (K) at 2.96 per 100 μmol/L. SUA, serum uric acid; BMD, bone mineral density; BMI, body mass index; 25(OH)D, 25-hydroxy vitamin D; BUN, blood urea nitrogen

BMD (β = 0.0029, 95%CI: -0.0200 to 0.0259, P = 0.8024). A positive linear relationship was nonetheless observed between SUA and BMD for patients with a BMI of 24–28 kg/m² or ≥ 28 kg/m² (P-value for LRT = 0.590, P-value for LRT = 0.498).

Discussion

Here, a cross-sectional analysis of 1,249 hospitalized OP patients revealed a significant positive correlation between SUA levels and BMD. Moreover, adjusted models revealed a non-linear association between these levels

Table 4 Threshold analyses examining the relationship between SUA levels and BMD

BMI	Model 3 ^a			
	< 24 kg/m ² β (95% CI) P-value	24–28 kg/m ² β (95% CI) P-value	≥ 28 kg/m ² β (95% CI) P-value	Total
Model A ^b				
One line effect	0.0239 (0.0118, 0.0361) 0.0001	0.0291 (0.0116, 0.0466) 0.0012	0.0500 (0.0251, 0.0749) 0.0001	P-interaction: 0.673 0.0286 (0.0193, 0.0378) < 0.0001
Model B ^c				
Serum uric acid turning point (K), per 100 μmol/L	2.96	1.91	4.98	P-interaction: 0.499 2.94
< K	0.0438 (0.0217, 0.0658) 0.0001	-0.0129 (-0.1679, 0.1422) 0.8709	0.0437 (0.0124, 0.0750) 0.0073	0.0413 (0.0229, 0.0598) < 0.0001
> K	0.0029 (-0.0200, 0.0259) 0.8024	0.0309 (0.0122, 0.0495) 0.0013	0.0827 (-0.0180, 0.1834) 0.1106	0.0187 (0.0032, 0.0342) 0.0184
Slope 2 – Slope 1	-0.0408 (-0.0788, -0.0029) 0.0352	0.0437 (-0.1167, 0.2041) 0.5936	0.0390 (-0.0775, 0.1555) 0.5130	-0.0226 (-0.0511, 0.0058) 0.1186
BMD value at K, g/cm ²	0.7621 (0.7453, 0.7788)	0.7491 (0.7241, 0.7741)	0.8663 (0.8097, 0.9229)	0.7748 (0.7621, 0.7875)
LRT test ^d	0.034	0.590	0.498	0.117

Abbreviations: SUA serum uric acid, BMD bone mineral density, CI confidence interval, BMI body mass index, 25(OH)D 25-hydroxy vitamin D, BUN blood urea nitrogen, LRT logarithmic likelihood ratio test

^a Adjusted for age, gender, 25(OH)D levels and BUN

^b Linear analysis, P-value < 0.05 indicates a linear relationship

^c Non-linear analysis

^d P-value < 0.05 means Model B is significantly different from Model A, which indicates a non-linear relationship

in individuals with a BMI < 24 kg/m², exhibiting an inflection point at 296 μmol/L of SUA among BMI. As such SUA levels may have a protective influence on BMD in certain settings, with BMI having the potential to influence the relationship between these two variables. While elevated SUA levels may offer some benefit to the BMD of OP patients, in patients with a BMI of less than 24 kg/m², SUA levels above 296 μmol/L may be unrelated to BMD.

Several epidemiological studies have explored the relationship between SUA and BMD, but the results have been inconsistent. Some reports suggest that SUA is significantly related to BMD and may have a protective impact on bone metabolism when assessing healthy adults [22], type 2 diabetes patients [23, 24], postmenopausal women [8, 25, 26], and elderly individuals [27]. However, some studies have demonstrated that there is no association between SUA and BMD in adult males in the USA [13], postmenopausal women [28], a rodent model of chronic mild hyperuricemia [29], or postmenopausal patients with type 2 diabetes [30]. These inconsistencies may be due to differences in the study populations. Our study found that SUA levels and BMD are independently positively associated, and we specifically focused on patients diagnosed with OP.

The mechanistic basis that links SUA to bone metabolism remains poorly defined, with some research attributing the protective benefits of SUA to its antioxidant activity. Indeed, SUA is an endogenous antioxidant, particularly under conditions of oxidative stress [9], and can readily scavenge free radicals in the plasma. In their review, Lin et al. determined that normal or elevated SUA concentrations were significantly related to reductions in BMD and exhibited protective effects against bone fracture [31]. ROS can readily suppress the differentiation of osteoblasts while enhancing osteoclastic differentiation and activation, ultimately leading to osteopenia [32]. SUA is associated with dose-dependent reductions in osteoclastogenesis and can suppress ROS production in osteoclast precursors [6]. UA also reportedly promotes human bone mesenchymal stem cell proliferation and osteoblastic differentiation while inhibiting the adipogenic differentiation of these cells [33]. In mice treated with oxonic acid, SUA exerts protective efficacy given that these animals exhibit reduced synovial infiltration by inflammatory cells, with corresponding decreases in synovial hyperplasia, bone erosion, and cartilage damage as compared to control animals [34]. Other factors may also explain the observed relationship between SUA and BMD, with muscle mass as one potential mediator of this relationship through processes related to muscle-derived cytokine production and mechanical loading [35]. There is thus a clear need for further studies exploring the

underlying mechanisms governing this relationship to firmly establish the value of SUA as a diagnostic biomarker associated with OP and other forms of disease. SUA exhibits paradoxical concentration-dependent effects, exhibiting beneficial antioxidant activity at normal concentrations but serving as a metabolic syndrome risk factor in the context of hyperuricemia [36]. A randomized controlled trial of postmenopausal women found that while supplemental inosine intake resulted in sustained serum urate concentrations over 6 months, it had no impact on bone turnover-related markers, in contrast with the concept that urate directly influences this bone turnover process [37].

In this study, a threshold effect was observed for the relationship between SUA levels and BMD in patients with a BMI < 24 kg/m². This finding is distinct from that of prior reports and suggests that in normal and lower-weight individuals, it may be important to maintain SUA levels within a desirable range (threshold: 296 μmol/L). Explaining the mechanistic basis for this phenomenon is difficult. We sought to explore differences in the association between SUA and BMD in different patient BMI subgroups. A positive association between BMI and BMD has been reported previously. BMI or weight can affect BMD as a result of the load factor [38]. According to Dalbeth et al., individuals with a high BMI exhibit reduced renal clearance after consuming dietary purines and have a larger renal capacity for UA reabsorption when fasting, with a higher BMI thus being associated with hyperuricemia [39]. It is thus possible that the positive relationship between UA and BMD is a consequence of obesity or higher BMI. However, one study found that ~25% of the effect of UA on BMD may be explained by BMI. While this BMI-mediated effect is statistically significant, a large portion of the role of UA in this context is thus not BMI-dependent [23]. In those patients with normal or lower weight, BMI-mediated effects may be less pronounced than in overweight or obese individuals. This may explain the reason why a threshold effect was only observed in patients with a BMI < 24 kg/m².

A recent review indicated that SUA levels can contribute to a higher risk of fracture in patients suffering from hyperuricemia or gouty arthritis, as the combination of oxidative stress and inflammatory cytokine production in response to SUA degradation simultaneously enhanced bone resorption while suppressing bone formation [31]. Antioxidative compounds can thus potentially undergo conversion into deleterious pro-oxidative compounds in certain contexts. Other work has also suggested that pro-oxidative SUA can cause damage in other disease-related settings [40]. Given this apparent paradoxical conflict between the harmful and beneficial effects of SUA, caution is necessary when translating these results

to the clinic. While the correction of hyperuricemia is important to lower the risk of other types of disease, it is important to guard against overtreatment which has the potential to mitigate the beneficial impact of SUA as a suppressor of oxidative stress. An individualized determination of optimal SUA levels should instead be made following the assessment of individual patient risk of OP and other diseases. The present results suggest that the BMI of patients should similarly be taken into consideration in this setting. Marin-Mio et al. reported a lower risk of OP in individuals that maintain a healthy muscle mass [41]. In the present analysis, SUA levels > 296 $\mu\text{mol/L}$ were found to have little impact on BMD in patients with a BMI < 24 kg/m^2 , potentially explaining why some prior analyses have failed to detect any relationship between these two clinical variables.

The results of this analysis may have important clinical implications. For one, the observed positive relationship between SUA levels and BMD suggests that higher levels are not necessarily beneficial, particularly among normal- and low-weight patients with OP beyond the identified threshold. This threshold may thus be of value in guiding SUA-focused clinical interventions and can aid in the formulation of appropriate treatment guidelines and clinical procedures for particular subsets of OP patients. Secondly, these results suggest that baseline SUA levels offer predictive value when assessing BMD in OP patients such that these levels have the potential to be incorporated into panels of fracture risk predictors in the context of patient clinical evaluation.

This study exhibits several important strengths. For one, the study population was rigorously screened. Additionally, the relationship between SUA levels and BMD was rigorously examined using four different models that were adjusted for a range of different potential confounding variables including age, gender, BMI, 25(OH)D levels, BUN, ALT, AST, Cr, and primary diagnosis. Moreover, differences in the association between SUA and BMD were observed in patients with a BMI < 24 kg/m^2 , potentially explaining prior controversy with respect to the relationship between these two variables in other studies.

There are some limitations to this analysis. For one, while SUA levels were found to be related to BMD in these patients, this does not offer any evidence of causality pertaining to this relationship. Moreover, other potentially relevant biochemical indicators including parathyroid hormone (PTH) and plasma phosphate levels were not analyzed in these patients and have the potential to impact bone metabolism. Markers of bone turnover such as procollagen type I N-terminal propeptide (P1NP) and cross linked C-telopeptide of type I collagen (CTX1) were similarly not analyzed. Third, this was a single-center study of a relatively small patient population such that these findings may not be generalizable to individuals of other ethnicities.

In light of these limitations, further large-scale follow-up studies incorporating additional biochemical markers, multi-ethnic populations, a multi-center randomized design will be critical to ensure that these results are robust and replicable. Future studies can additionally focus on the role of BMI in the relationship between SUA and BMD and the mechanisms underlying this relationship.

Conclusions

In summary, the results of this analysis indicate that SUA levels and BMD are independently positively associated with one another in patients with OP. A non-linear relationship between SUA levels and BMD was also observed in patients with both normal and low body weight, suggesting that these SUA levels may offer protective value for BMD in both normal- and low-weight individuals with OP. Specifically, while SUA levels below 296 $\mu\text{mol/L}$ were predicted to be protective, values above these levels were not associated with BMD. However, additional follow-up research with a larger number of patients will be critical to validate these findings.

Abbreviations

SUA	Serum uric acid
BMD	Bone mineral density
BMI	Body mass index
CI	Confidence interval
OP	Osteoporosis
ROS	Reactive oxygen species
ZOL	Zoledronic acid
DXA	Dual-energy X-ray absorptiometry
CCI	Charlson comorbidity index
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
Cr	Creatinine
BUN	Blood urea nitrogen
25(OH)D	25-Hydroxy vitamin D
SD	Standard deviations
GEE	Generalized estimating equations
VIF	Variance inflation factor
OR	Odds ratio
GAM	Generalized additive model
LRT	Likelihood ratio test

Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s12891-023-06414-w>.

Additional file 1.

Additional file 2.

Acknowledgements

None.

Authors' contributions

KL, QS and CL designed the study. CL and KL conducted the study. MZX, KL, XFY, YWY, SMX, YQG collected the data. MZX and YQG analysed the data. MZX and KL interpreted the data. MZX drafted the main manuscript. QS and KL Revised the main manuscript content. CL, KL, QS and YQG approved final version of manuscript. MZX and KL take responsibility for the integrity of the

data analysis. MXZ and KL contributed equally to this work and should be considered co-first authors. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. The author(s) read and approved the final manuscript.

Funding

The study was supported by National Natural Science Foundation of China (CN) (82172441), Elderly Health Research Project of Jiangsu Province (CN) (LKZ2022020), Suzhou Collaborative Innovation Research Project of Medical and Industrial Integration (CN) (SLJ2022023), Clinical Medical Science and Technology Development Fund of Jiangsu University (CN) (JLY2021048) and Suzhou Key Clinical Diagnosis and Treatment Technology Project (CN) (LCZX202024).

Availability of data and materials

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

This is a retrospective observational study, based on medical data from a clinical registry. This work is registered in the Chinese Clinical Trial Registry (ChiCTR2000036375, registration date: 22/08/2020). In addition, we received ethical approval from the Affiliated Kunshan Hospital of Jiangsu University (approval No. 2020-03-046-K01), and the study was compliant with the Declaration of Helsinki. The informed consent was waived by the Ethics Committee of the Affiliated Kunshan Hospital of Jiangsu University.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

¹Department of Orthopedics, Affiliated Kunshan Hospital of Jiangsu University, Suzhou 215300, Jiangsu, China. ²Department of Orthopedics, Gusu School, Nanjing Medical University, The First People's Hospital of Kunshan, Suzhou, Jiangsu 215300, China. ³Department of Orthopedics, the First Affiliated Hospital of Soochow University, Orthopedic Institute of Soochow University, Suzhou 215031, Jiangsu, China. ⁴Information Department, Affiliated Kunshan Hospital of Jiangsu University, Suzhou 215300, Jiangsu, China.

Received: 27 November 2022 Accepted: 10 April 2023

Published online: 18 April 2023

References

- Lane NE. Epidemiology, etiology, and diagnosis of osteoporosis. *Am J Obstet Gynecol.* 2006;194(2 Suppl):S3-11.
- Dong Y, Kang H, Peng R, Song K, Guo Q, Guan H, et al. Global, regional, and national burden of low bone mineral density from 1990 to 2019: results from the global burden of disease study 2019. *Front Endocrinol (Lausanne).* 2022;13:870905.
- Reginster JY, Burlet N. Osteoporosis: a still increasing prevalence. *Bone.* 2006;38(2 Suppl 1):S4-9.
- Yao X, Chen L, Xu H, Zhu Z. The association between serum uric acid and bone mineral density in older adults. *Int J Endocrinol.* 2020;2020:3082318.
- Xiao J, Chen W, Feng X, Liu W, Zhang Z, He L, et al. Serum uric acid is associated with lumbar spine bone mineral density in healthy Chinese males older than 50 years. *Clin Interv Aging.* 2017;12:445-52.
- Ahn SH, Lee SH, Kim BJ, Lim KH, Bae SJ, Kim EH, et al. Higher serum uric acid is associated with higher bone mass, lower bone turnover, and lower prevalence of vertebral fracture in healthy postmenopausal women. *Osteoporos Int.* 2013;24(12):2961-70.
- Ishii S, Miyao M, Mizuno Y, Tanaka-Ishikawa M, Akishita M, Ouchi Y. Association between serum uric acid and lumbar spine bone mineral density in peri- and postmenopausal Japanese women. *Osteoporos Int.* 2014;25(3):1099-105.
- Han W, Bai X, Han L, Sun X, Chen X. Association between higher serum uric acid levels within the normal physiological range and changes of lumbar spine bone mineral density in healthy Chinese postmenopausal women: a longitudinal follow-up study. *Menopause.* 2021;28(10):1157-65.
- Glantzounis GK, Tsimoyiannis EC, Kappas AM, Galaris DA. Uric acid and oxidative stress. *Curr Pharm Des.* 2005;11(32):4145-51.
- Waring WS, Webb DJ, Maxwell SR. Systemic uric acid administration increases serum antioxidant capacity in healthy volunteers. *J Cardiovasc Pharmacol.* 2001;38(3):365-71.
- Kaushal N, Vohora D, Jalali RK, Jha S. Review of the literature examining the association of serum uric acid with osteoporosis and mechanistic insights into its effect on bone metabolism. *Endocr Metab Immune Disord Drug Targets.* 2019;19(3):259-73.
- Chen F, Wang Y, Guo Y, Wang J, Yang A, Lv Q, et al. Specific higher levels of serum uric acid might have a protective effect on bone mineral density within a Chinese population over 60 years old: a cross-sectional study from northeast China. *Clin Interv Aging.* 2019;14:1065-73.
- Li X, Li L, Yang L, Yang J, Lu H. No association between serum uric acid and lumbar spine bone mineral density in US adult males: a cross-sectional study. *Sci Rep.* 2021;11(1):15588.
- Camacho PM, Petak SM, Binkley N, Diab DL, Eldeiry LS, Farooki A, et al. American association of clinical endocrinologists/American college of endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis-2020 update. *Endocr Pract.* 2020;26(Suppl 1):1-46.
- Ho YV, Frauman AG, Thomson W, Seeman E. Effects of alendronate on bone density in men with primary and secondary osteoporosis. *Osteoporos Int.* 2000;11(2):98-101.
- Glaser DL, Kaplan FS. Osteoporosis. Definition and clinical presentation. *Spine (Phila Pa 1976).* 1997;22(24 Suppl):12S-16S.
- Fitzpatrick LA. Secondary causes of osteoporosis. *Mayo Clin Proc.* 2002;77(5):453-68.
- Zhou BF. Predictive values of body mass index and waist circumference for risk factors of certain related diseases in Chinese adults—study on optimal cut-off points of body mass index and waist circumference in Chinese adults. *Biomed Environ Sci.* 2002;15(1):83-96.
- Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40(5):373-83.
- Kernan WN, Viscoli CM, Brass LM, Broderick JP, Brott T, Feldmann E, et al. Phenylpropanolamine and the risk of hemorrhagic stroke. *N Engl J Med.* 2000;343(25):1826-32.
- Liu S, Wang X, Lu Y, Li T, Gong Z, Sheng T, et al. The effects of intraoperative cryoprecipitate transfusion on acute renal failure following orthotopic liver transplantation. *Hepatol Int.* 2013;7(3):901-9.
- Ibrahim WN, Younes N, Shi Z, Abu-Madi MA. Serum uric acid level is positively associated with higher bone mineral density at multiple skeletal sites among healthy Qataris. *Front Endocrinol (Lausanne).* 2021;12:653685.
- Xu M, Su J, Hao J, Zhong N, Zhang Z, Cui R, et al. Positive association between serum uric acid and bone mineral density in Chinese type 2 diabetes mellitus stratified by gender and BMI. *J BONE MINER METAB.* 2018;36(5):609-19.
- Yan P, Zhang Z, Wan Q, Zhu J, Li H, Gao C, et al. Association of serum uric acid with bone mineral density and clinical fractures in Chinese type 2 diabetes mellitus patients: a cross-sectional study. *Clin Chim Acta.* 2018;486:76-85.
- Beyazit F, Pek E. Effects of vitamin B12, folate, uric acid, and serum biomarkers of inflammation on bone mineral density in postmenopausal women. *Prz Menopauzalny.* 2018;17(2):69-76.
- Han W, Bai X, Wang N, Han L, Sun X, Chen X. Association between lumbar bone mineral density and serum uric acid in postmenopausal women: a cross-sectional study of healthy Chinese population. *Arch Osteoporos.* 2017;12(1):50.
- Babaei M, Shamsi R, Heidari B, Bijani A, Hosseini SR. Serum uric acid status and its association with bone mineral density in the elderly people aged 60 years and more. *Int J Endocrinol Metab.* 2019;17(3):e80780.
- Kang S, Kwon D, Lee J, Chung YJ, Kim MR, Namkung J, et al. Association between serum uric acid levels and bone mineral density in postmenopausal women: a cross-sectional and longitudinal study. *Healthcare (Basel).* 2021;9(12):1681.

29. Zhang D, Bobulescu IA, Maalouf NM, Adams-Huet B, Poindexter J, Park S, et al. Relationship between serum uric Acid and bone mineral density in the general population and in rats with experimental hyperuricemia. *J BONE MINER RES.* 2015;30(6):992–9.
30. Zhao X, Yu X, Zhang X. Association between uric acid and bone mineral density in postmenopausal women with type 2 diabetes mellitus in China: a cross-sectional inpatient study. *J Diabetes Res.* 2020;2020:3982831.
31. Lin KM, Lu CL, Hung KC, Wu PC, Pan CF, Wu CJ, et al. The paradoxical role of uric acid in osteoporosis. *Nutrients.* 2019;11(9):2111.
32. Lee HS, Hwang JS. Impact of type 2 diabetes mellitus and antidiabetic medications on bone metabolism. *Curr Diab Rep.* 2020;20(12):78.
33. Li HZ, Chen Z, Hou CL, Tang YX, Wang F, Fu QG. Uric acid promotes osteogenic differentiation and inhibits Adipogenic differentiation of human bone mesenchymal stem cells. *J Biochem Mol Toxicol.* 2015;29(8):382–7.
34. Lai JH, Luo SF, Hung LF, Huang CY, Lien SB, Lin LC, et al. Physiological concentrations of soluble uric acid are chondroprotective and anti-inflammatory. *Sci Rep.* 2017;7(1):2359.
35. Dong XW, Tian HY, He J, Wang C, Qiu R, Chen YM. Elevated serum uric acid is associated with greater bone mineral density and skeletal muscle mass in middle-aged and older adults. *PLoS ONE.* 2016;11(5):e154692.
36. Zhang Q, Zhang C, Song X, Lin H, Zhang D, Meng W, et al. A longitudinal cohort based association study between uric acid level and metabolic syndrome in Chinese Han urban male population. *BMC Public Health.* 2012;12:419.
37. Dalbeth N, Horne A, Mihov B, Stewart A, Gamble GD, Merriman TR, et al. Elevated urate levels do not alter bone turnover markers: randomized controlled trial of inosine supplementation in postmenopausal women. *Arthritis Rheumatol.* 2021;73(9):1758–64.
38. Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: the Framingham study. *J Bone Miner Res.* 1993;8(5):567–73.
39. Dalbeth N, Allan J, Gamble GD, Horne A, Woodward OM, Stamp LK, et al. Effect of body mass index on serum urate and renal uric acid handling responses to an oral inosine load: experimental intervention study in healthy volunteers. *Arthritis Res Ther.* 2020;22(1):259.
40. Lippi G, Montagnana M, Franchini M, Favalaro EJ, Targher G. The paradoxical relationship between serum uric acid and cardiovascular disease. *Clin Chim Acta.* 2008;392(1–2):1–7.
41. Marin-Mio RV, Moreira L, Camargo M, Perigo N, Cerondoglo MS, Lazaretti-Castro M. Lean mass as a determinant of bone mineral density of proximal femur in postmenopausal women. *Arch Endocrinol Metab.* 2018;62(4):431–7.

Publisher's Note

Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Ready to submit your research? Choose BMC and benefit from:

- fast, convenient online submission
- thorough peer review by experienced researchers in your field
- rapid publication on acceptance
- support for research data, including large and complex data types
- gold Open Access which fosters wider collaboration and increased citations
- maximum visibility for your research: over 100M website views per year

At BMC, research is always in progress.

Learn more biomedcentral.com/submissions

